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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,084	10/24/2001	Avi J. Ashkenazi	GNE.2630P1C66	4358

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,084	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-65,68-70,74-77,86 and 87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *63-65 and 68-70* is/are allowed.

6)☒ Claim(s) *59-62, 74-77, 86 and 87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.t.O.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 April 2005 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. This Office Action contains New grounds of Rejections.

4. Claims 59-65, 68-70, 74-77 and 86-87 are pending and under examination.

Objections/Rejections Withdrawn

5. All objections/rejections presented in the previous Office Action mailed 13 January 2005 are withdrawn in view of applicant's arguments and amendments to the claims in the response filed 12 April 2005.

New grounds of Rejections

6. Claims 61-62 and 74-77 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 61-62 and 74-77 are indefinite for reciting "the amino acid sequence of the full-length coding sequence of the nucleic acid sequence..." in parts (b) and (c) of claim 61 and parts (c) and (d) of claim 62. It is unclear what is contemplated by the phrase because an amino acid sequence and a nucleic acid sequence are chemically distinct molecules. While those of skill in the art recognize that nucleic acids encode amino acid sequences, the two molecules are chemically different and not considered as equivalents. Thus, the recitation that "the amino acid sequence of the full-length coding sequence of the nucleic acid sequence..." is unclear and one of skill in the art would not be reasonably apprised of the metes and bounds of the phrase or molecules embraced by said phrase.

b. Claim 74 recites the limitation "the nucleic acid". There is insufficient antecedent basis for this limitation in the claim. It is unclear if "the nucleic acid" refers to the specific nucleic acids recited in parts (a), (b), (c) or (d) of claims 59-62 or if "the nucleic acid" refers to the "isolated nucleic acid" having the claimed sequence identity to the nucleic acids of parts (a), (b), (c) or (d) of claims 59-62.

7. Claims 59-62, 74-77 and 86-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to isolated nucleic acids having at least 85% sequence identity with the nucleic acid sequence of SEQ ID NO:522 or having at least 90% sequence identity with the full-length coding sequence of SEQ ID NO:522 and isolated nucleic acids encoding a polypeptide having at least 95% amino acid identity with SEQ ID NO:523, optionally lacking its associated signal peptide or the amino acid sequence encoded by the full-length coding sequence of SEQ ID NO:522, wherein the polypeptide or encoded polypeptide is a mitogen for inner ear supporting cells.

The specification discloses that the PRO337 polypeptide (i.e., SEQ ID NO:523 encoded by SEQ ID NO:522) is a newly identified member of the IgLON sub family of the immunoglobulin suprefamily and may posses neurite growth and differentiation potentiating properties (see page 179). The specification discloses that the PRO337 polypeptide was positive for the proliferation of rat utricular supporting cells (assay 54 at page 347) and thus, acts as a mitogen for inner ear supporting cells.

The specification does not provide sufficient written description as to the structural features of the claimed genus of PRO337 nucleic acids and encoded polypeptides and the correlation between the chemical structure and function of the genus of PRO337 nucleic acids, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded. The specification does not disclose a single species with less than 100% sequence identity with the PRO337 nucleic acids or encoded polypeptides..

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is

substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for identifying a PRO337 nucleic acid

encompassed by the claimed specificity. For example, there is insufficient guidance based on the reliance of disclosure of SEQ ID NO:522 to direct a person of skill in the art to select or to predict particular sequences as essential for identifying PRO337 nucleic acids encompassed by the claimed specificities. Mere idea of function is insufficient fro written description; isolation and characterization at a minimum are required.

Scholnick et al (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based on sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to function of the structurally related protein (see in particular "Abstract" and Box 2).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138, cited on PTO-892 mailed 11/13/2003). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar

et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252, cited on PTO-892 mailed 11/13/2003).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance on the activity of the PRO337 polypeptide encoded by SEQ ID NO:522 disclosed in the specification as-filed does not appear to provide sufficient written description for the genus of nucleic acids encompassed by the claimed specificities in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single species encompassed by the highly variant genus nor is there disclosure of the common attributes or features (i.e., structural domains) that are essential for activity or those which are non-essential. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddles v.Baird*, 30 USPQ2d 1481, 1483. In *Fiddles v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids comprising SEQ ID NO:522 and nucleic acids encoding SEQ ID NO:523, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

8. Claims 59-62, 74-77 and 86-87 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for isolated nucleic acids comprising SEQ ID NO:522 and nucleic acids encoding the polypeptide of SEQ ID NO:523, does not reasonably provide enablement for isolated nucleic acids having at least 85% sequence identity with the nucleic acid of SEQ ID NO:522 or nucleic acids encoding a polypeptide having at least 95% sequence identity with the amino acid sequence of SEQ ID NO:523. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to isolated nucleic acids having at least 85% sequence identity with the nucleic acid sequence of SEQ ID NO:522 or having at least 90% sequence identity with the full-length coding sequence of SEQ ID NO:522 and isolated nucleic acids encoding a polypeptide having at least 95% amino acid identity with SEQ ID NO:523, optionally lacking its associated signal peptide or the amino acid sequence encoded by the full-length coding sequence of SEQ ID NO:522, wherein the polypeptide

or encoded polypeptide is a mitogen for inner ear supporting cells. Applicants have taught the polypeptide of SEQ ID NO:523, which is encoded by SEQ ID NO:522, is a newly identified member of the IgLON sub family of the immunoglobulin suprefamily and may posses neurite growth and differentiation potentiating properties (see page 179). The specification discloses that the PRO337 polypeptide was positive for the proliferation of rat utricular supporting cells (assay 54 at page 347) and thus, acts as a mitogen for inner ear supporting cells. However, Applicants provide little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the PRO337 protein that are tolerant to change and the nature and extent of changes that can be made in these positions. There is no exemplary guidance presented in the specification to assist one skilled in the art in making and using the variants having the claimed specificity.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects and finally what changes can be tolerated with respect thereto is complex and well outside the

realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al. (1990), Science 247:1306- 1310, especially p. 1306, column 2, paragraph 2; Wells (1990), Biochemistry 29: 8509-8517; Ngo et al. (1994), The Protein Folding Problem and Tertiary Structure Prediction, Merz et al., eds., Birkhauser, Boston, pp. 492-495).

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue

experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Conclusion

9. Claims 63-65 and 68-70 are free of the prior art and are in condition for allowance.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS,
PRIMARY EXAMINER